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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/721,563	11/25/2003	Tal Kafri	9435-2	5850

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EXAMINER	
BURKHART, MICHAEL D	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 07/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/721,563	KAFRI ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/5/2006.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 5-10, 12-17, 19-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) 5-8,12-15 and 19-23 is/are allowed.

6)☒ Claim(s) 9, 10, 16, 17, and 24-29 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendments dated 1/18/2006 and 5/5/2006 is acknowledged. After entry of the amendments, claims 5-10, 12-17, and 19-29 are pending. Claims 5 and 13 are directed to allowable products. Pursuant to the procedures set forth in MPEP § 821.04(B), claims 24-29, directed to processes of making or using the allowable products, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, the restriction requirement as set forth in the Office action mailed on 3/24/2005 is hereby withdrawn. In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claims including all the limitations of an allowable product claim or rejoined process claim are presented in a continuation or divisional application, such claims may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: claim 20 recites a "circular retroviral form plasmid" in lines 1-2. There is no antecedent basis for this term in the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These new rejections were necessitated by amendment of the claims.**

Claims 24 and 27 are rejected as being indefinite for failing to recite a positive process step that refers back to the preamble of the claim. In order for the claimed method to be definite in terms of the metes and bounds of the invention, the claim must recite a method step that provides for the results of the method as claimed. Claims 24 and 27 recite, in lines 1-2, methods wherein a gene product results in a particular phenotype upon contact with a test substance. However, in step c) of each claim, cells are indicated as being contacted with the test substance. Furthermore, there is no reference in the remainder of the claims to contacting the gene product with the test substance. Therefore, it is unclear what actually needs to be contacted with the test substance to meet the claim limitations: the gene product or the cells. Contacting the cells does not necessarily lead to contacting the gene product with the test substance, and still may result in a particular phenotype (e.g. through a signaling pathway not directly involving the gene product). For this reason, the metes and bounds of the claimed subject matter are unclear. This rejection affects all dependent claims.

Claims 24 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps.

See MPEP § 2172.01. The omitted steps are: selection of the cells recited in step (c) of each claim. Step (d) of each claim recites the "surviving cells of step (c)", strongly implying that there was some selective pressure placed on the cells of step (c). However, there is no recitation of a selection step, nor is it clear why all the cells of step (c) would not survive if there were no such step. This rejection affects all dependent claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 10, 16, and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by amendment of the claims. This is a New Matter rejection.**

Amended claims 9 and 16 (from which the other rejected claims depend) recite nucleic acids comprising, *inter alia*, a U3 region of an LTR with a *loxP* site, wherein enhancer and promoter sequences of the U3 are deleted and minimal sequences required for integration at the 5' end of the LTR are not deleted, and the *loxP* site is not deleted. The response indicates support for the amendment may be found in the original claims and ¶'s [0055] and [0056]. These passages do not recite the claimed nucleic acid wherein the U3 has the above deletions and a *loxP* site, but rather teach that the claimed nucleic acids may comprise the above deletion(s) in

the U3, which deletions may be in the form of replacement with an inducible promoter. The following ¶ discloses that the U3 region of the claimed nucleic acids may comprise a *loxP* site or a restriction site. A reading of the remainder of the specification reveals that there are no teachings that these two modification of the U3 could be used together, and such a situation is not found in any of the vector diagrams as provided in the Figures. Thus, there is no evidence that applicants considered their invention to encompass nucleic acids wherein the said portions of U3 are deleted or retained and a *loxP* site is within the U3. Thus, the amended claims include impermissible New Matter.

Claims 24-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics,* Inc. 8 USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art. The art concerning isolating a certain cDNA sequence from a library of such sequences in the context of the nucleic acid construct as recited in claim 5 is unpredictable. This is because the claimed nucleic acid construct (essentially a retroviral cloning vector) has no means of reproducing itself or integrating into a host chromosome when

introduced into eukaryotic cells in DNA form, as instantly claimed. In eukaryotic cells, the individual members of such a cDNA library would not be passed onto daughter cells because the library members have no way to replicate or integrate. This leads to eventual loss of the cDNA library, as the host cells originally comprising the cDNA library die or are replaced by daughter cells. The claimed nucleic acid has no eukaryotic origin of replication, and to function as claimed depends upon being introduced into a host cell as a viral genome in order that viral enzymes for reverse transcription and integration may complete the "viral" life cycle and integrate the library members into the host chromosome. Once in the host chromosome, the library members are replicated and passed one to daughter cells like any other region of host chromosomal DNA. Thus, the host cell essentially becomes a stable cell line, and is suitable for downstream applications, such as detailed in the remainder of claims 24 and 27. The concept of using retroviral vectors to express and probe cDNA or genetic libraries is illustrated in two papers using highly related technology, Ma et al (Mol. Therapy, 2004) and Hannon et al (Science, 1999). Hannon et al teach the MaRX system (Fig. 1), in which a DNA library is converted into a library of retroviruses that are used to infect recipient cells, which cells are then selected or enriched based on a biological property (i.e. step (c) of the instant claims). Relevant to the instant rejection, Hannon et al state that "stable integration of recombinant retroviruses allows phenotypes to be assessed over many cell generations" (page 129, third column, first full ¶). Ma et al teach retroviral vectors essentially as recited in claim 5 (see Fig. 1A). The vectors were used to produce retroviral particles that were used to infect 293T cells, which then expressed any transgene within the vector(s), one example being found in the ¶ bridging pages 144-145, which used the blastocidin resistance transgene. The transgene could then be recovered

from the eukaryotic cells upon *Cre* expression. Ma et al also list "stable integration of the genetic cargo" as an attribute of using retroviruses for this purpose (page 139, first column, second ¶). Thus, the cited art underscores the necessity of using a retroviral particle to deliver the claimed nucleic acids into cells in order for stable integration of the transgene (and other vector elements) to occur, which is required for the claimed downstream steps to work, i.e. selecting a desired phenotype/cDNA.

State of the art. The state of the art regarding isolating a certain cDNA sequence from a library of such sequences in the context of the nucleic acid construct as recited in claim 5, when not integrated into a host chromosome, is poorly developed. The development of such vectors, cells and methods would have to be done empirically.

Number of working examples. Applicants have provided no working examples of isolating a certain cDNA sequence from a library of such sequences in the context of the nucleic acid construct as recited in claim 5, when not integrated into a host chromosome. All of the working examples involve preparing retroviruses bearing the nucleic acids as an RNA genome, which, after infection of a host cell, is subsequently integrated into the host chromosome.

Amount of guidance. Applicants provide no direction or guidance for the claimed methods when the cDNA is not integrated into the host chromosome. The specification requires the skilled artisan to practice trial and error experimentation with different vectors, cells and method steps to determine which (if any) will be function as claimed.

Scope of the invention. The claims are broad in nature and read on selecting any gene product from any cDNA, from a cDNA library from any tissue source, using any host cell and structural components from any lentivirus.

Nature of the invention. The invention involves the unpredictable art of isolating a certain cDNA sequence from a library of such sequences in the context of the nucleic acid construct as recited in claim 5, when not integrated into a host chromosome.

Level of skill in the art. While the level of skill in the art is high, the unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Conclusion

Claims 5-8, 12-15, and 19-23 are allowed. Any rejection not repeated in this Office Action is withdrawn.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

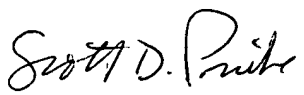
will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael D. Burkhart
Examiner
Art Unit 1633



SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER